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OF THE

PATHOLOGICAL SOCIETY

OF

PHILADELPHIA

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Proceedings

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DR. EDWARD O. SHAKESPEARE.

At a meeting of the Pathological Society held on October 25, 1900, the undersigned committee presented the following minute which was adopted and ordered printed in the PROCEEDINGS of the Society:

Edward O. Shakespeare was born May 19, 1846, and died June 1, 1900. Gifted by nature with talents of the highest order, he so used them as to leave an indelible impression upon medical science. His interests were wide, and embraced ophthalmology, histology, pathology, bacteriology, and sanitary science. In addition, he was a linguist, a skilful etcher on stone, and a master of the art of photography, particularly of that difficult branch, microphotography.

As an ophthalmologist, he was not only a conscientious and successful practitioner, particularly in hospitals, but also a scientist and an inventor, having devised, among other things, an ophthalmoscope for use in the study of the eyes of human beings and animals.

The thorough knowledge of histology which he possessed is shown in the splendid chapter on that subject contributed by him to Harrison Allen's *Anatomy*. His researches in pathology are

largely contained in the TRANSACTIONS of this Society, of which he was President in 1884 and 1885, and in various articles contributed to medical journals; in the translation of Cornil and Ranvier's *Manual of Pathological Histology*, and in the *Toner Lecture* of 1879, in which he dealt with the nature of the reparatory changes in arteries after ligation, acupressure, and torsion.

In later years his chief interest was centered in bacteriology, and it is his work in this science that will forever constitute the pedestal of his fame. His able defence of the specificity of the tubercle bacillus against the powerful assaults of Dr. Formad and others was based upon a thorough knowledge of the subject, and attracted the widest attention.

As a sanitarian he will always be remembered for his masterly study of the typhoid fever epidemic at Plymouth, Pennsylvania, by which he was able to demonstrate beyond cavil the water-borne character of the disease, and for his exhaustive researches on cholera made under the auspices of the United States Government in 1885 and 1886. His official report, in the preparation of which he spent four years, and for which he received no pecuniary remuneration, comprises 899 quarto pages and 105 illustrations, nearly all original. It is a monumental work—the most comprehensive one ever written upon the subject—and will remain an enduring exemplar for future investigators in the domain of epidemiology.

D. RIESMAN,
J. H. MUSSER,
W. E. HUGHES,
Committee.

Address of the President.

FREDERICK A. PACKARD, M.D.

According to custom and to a provision of the by-laws, upon the last meeting of his term of office the President of the Pathological Society delivers an annual address. This is apparently intended to give a summary of the work done during the year, and to pat ourselves upon the back or make anew good resolutions in accord-

ance with the results of the year's work. Glancing at the year as a whole, it will be found that it has been quite a successful one. We have held nineteen meetings, with an average attendance of thirty-two, showing, therefore, no falling off in the interest of the members. Most of these were the regular stated monthly meetings, with volunteer reading of papers and exhibition of specimens. These numbered eighty, or an average of about five papers or specimens at each meeting. The two exceptions were our annual conversational meeting, which was held in April, and at which an address was delivered by Dr. Theobald Smith upon "Comparative Pathology; Its Relation to Biology and Medicine," and another meeting out of the ordinary, which was held in January, and was occupied by a Symposium on Typhoid Fever. Dr. Theobald Smith's paper was a scholarly address upon a subject which is attaining more and more wide and deserved attention. The Symposium on Typhoid Fever was one calculated to interest alike the hygienist, the clinical pathologist, and the practising physician. The meeting was sufficiently successful both in the character of the papers read, the scope of the subject that was covered, and the attendance upon the meeting to make it seem advisable that the Business Committee should arrange for similar meetings in the future.

Before speaking of the actual papers read at our ordinary meetings, I would like to refer to what has been mentioned in the annual address of my predecessor—the publication of our *TRANSACTIONS* in the form of monthly fasciculi. The method has proven most satisfactory, as is evidenced by the expressions of opinion by members of the Society, by the frequency with which abstracts of our proceedings are found in the various foreign journals, and by the improvement in the character of the papers that follow upon the knowledge that they will appear without delay and before the subject-matter of the paper has had time to grow stale. By the present method of publication we get less of an idea as to the amount of work done in particular lines, owing to the fact that with the separate fasciculi we lose the grouping in regard to subjects which gave at a glance the amount of work done upon particular lines during the period covered by the bound volume of the *TRANSACTIONS* as it appeared formerly. It has seemed to me,

therefore, that this want might be somewhat supplied by a *résumé* of some of the papers in the Presidential Address. The only difficulty in doing this has been that it seems somewhat invidious to designate particular papers. A *résumé* of all the contributions would, of course, be out of place, yet I think it is a pardonable matter for us to see to what extent the work brought before us is contributing to the advancement of knowledge in the various important subjects in regard to pathology that are at present receiving most attention.

On looking over old volumes of the TRANSACTIONS OF THE PATHOLOGICAL SOCIETY there are found to be a fair number of exhibitions of specimens illustrating comparative pathology. To the Business Committee this has always seemed to be a branch deserving of our encouragement in arranging for the meetings for the year, and it is a notable fact that when specimens have been presented the interest of the members in coming forward to examine them has always been very evident. During this year there have not been presented as many specimens of this kind as we might hope to have. Those that have been shown have been the organs of a lioness which died of suffocation from impaction of meat in the larynx; a series of frogs presenting interesting and remarkable congenital anomalies, and a noteworthy specimen of aneurysm occurring in a chicken. It is to be hoped that during the next year more specimens of this character will be exhibited, particularly from the fact that comparative pathology is occupying a more and more prominent place, especially since its bearing upon human pathology has been particularly pointed out by such workers as Bland Sutton and others who have shown the relationship between disease in the human being and what were at one time considered as matters of interest only to students of natural history. We have been fortunate in having during the past year several results of experimental studies presented to us; among these I would particularly mention the paper of Flexner upon experimental pancreatitis, which throws additional light upon this but little understood pathologic condition.

The relation of tuberculosis to various species of animals is a subject that is of extreme importance, not only because of its general

interest, but because of its bearing upon questions of hygiene. The use of goats' milk for the nourishment of children has been urged, partly because this animal is supposed to be but little prone to tuberculosis. Ravenel and White have shown us specimens of the experimental production of tuberculosis produced by the inoculation of pure cultures of tubercle bacilli from a cow through the chest-wall into the lung of a goat. The importance of this observation can be readily seen when we bear in mind that autopsies upon goats are seldom conducted with such care as to enable us to get at the exact danger involved in using the milk of this animal in the nourishment of children.

Another point of interest to the hygienist is covered by a paper by Ravenel upon "The Transmission of Syphilis to Calves." This is particularly timely now, because of the idiotic attacks of the antivaccinationists upon the propriety of protection from small-pox. Ravenel's failure in two cases to produce the disease by the inoculation of the syphilitic virus is a valuable contribution to contradict the absurd claims of a set of fanatics, that "loathsome diseases," by which, in the majority of cases, they mean syphilis, can be inoculated with the material of the vaccine.

The paucity of articles dealing with bacteriology that have been read during the past year is doubtless due to the absence of proper means of demonstration at our meetings. Could we have a proper projection-apparatus by which slides could be thrown upon a screen, doubtless many more papers dealing with bacteriology would be presented. Among other papers which incidentally have dealt with the subject of bacteriology and allied subjects are those of Walsh, describing a sarcina pathogenic for guinea-pigs, which was obtained from the spleen of a child; a paper by Pearson and Ravenel upon pneumonormycosis due to the *aspergillus fumigatus*, and a paper by McFarland upon the bacillus of plague, a subject that is one of very active interest at the present time. Among the infections that have been dealt with in the papers that have been read during the year, or of which specimens have been shown, are typhoid fever, typhus fever, cerebrospinal meningitis, anthrax, bubonic plague, rabies, and tuberculosis. The preliminary report upon the rapid diagnosis of rabies, made by Ravenel and McCarthy at the meeting of June 14th, is of value in

confirming the work of Nelis and Van Gehuchten as to the changes in the intervertebral ganglia of the spinal cord. The importance of some means of rapid and certain determination of the existence of true hydrophobia makes such work as that covered by the article of much value, which will probably be greater in the future when our means of combating the disease are more established, while by an exact method of making a pathologic diagnosis the claims that are constantly being advanced that there is no such disease among the human species may be either confirmed or refuted.

At a recent meeting tuberculosis in cats was the subject of a paper, and we have had presented at one of our meetings specimens of cutaneous tuberculosis apparently proven to have been due to inoculation by the bovine bacillus, a question that is of much interest at the present time, when doubt is being thrown upon the identity of the bacillus producing tuberculosis in man and in the lower animals. Somewhat allied to this last paper was the one upon tuberculosis of the skin of the hand, reported by Schamberg.

The subject of internal secretions, and especially the existence and nature of an internal secretion from the pancreas and its connection with diabetes mellitus, makes this organ one of the most important subjects of study at the present time. We have had several interesting specimens of pancreatic disease presented at our meetings, beside the specimen of experimental inflammation of that gland that accompanied the paper of Flexner, mentioned above. The physiology and pathology of the suprarenal capsules are still sufficiently in the dark to make these organs extremely interesting objects of study, not only from the stand-point of physiology and pathology, but also because of the use of suprarenal extract as a drug. Specimens from two cases of Addison's disease have been shown, one from a negro; we have also had before us an example of hemorrhagic infiltration of the suprarenals and kidneys from an infant.

Among other papers dealing with the central nervous system, of which we have had quite a large number, I would mention as particularly valuable the "Report of a Case of Polioencephalomyelitis Presenting the Appearance of Landry's Disease," following a dissecting wound; specimens from a case of hematomyelia; exhibition of the malarial parasites in the capillaries of the central

nervous system, and a specimen of a tumor of the pituitary body found in a case of adiposis dolorosa.

Of illustrations of diseases of the circulatory system we have had a large and interesting number presented. I would especially call attention to the paper by Meigs upon "Endophlebitis," which is an elaborate study upon a subject that has received but little attention.

Owing to the activity of our surgical friends the appendix is more frequently seen than if we had to depend upon autopsies for obtaining a supply. Useless as the organ is in our economies, it has been the subject of extremely interesting papers during the past year. Of these I would particularly mention a paper by Kelly upon tumors of the vermiform appendix, and an elaborate article by Jopson upon hernia of this portion of the intestine.

When we bear in mind that in addition to those papers to which I have briefly alluded we have had the usual run of specimens occurring in the daily work of the members, it will be seen that we have had a very active year and one of which we may well be proud.

There are two ways in which it seems to me we might improve the field of our work. One of these has already been alluded to—I refer to the use of a projection-apparatus and screen. This would enable us to save a great deal of time which is now lost by the members coming forward to examine specimens under the microscopes. While this is time well spent, it is evident that something must be done to facilitate matters, especially as there is a constantly growing and very gratifying increase in the number of histologic specimens exhibited, either independently or with the gross lesions.

Another feature upon which we might lay more stress is the exhibition of card specimens. Between the autopsies at the various hospitals and those made in private practice a very large number of specimens are obtained each week in this city. The rarer specimens are at times shown in the fresh condition; many, however, of those of greatest interest are placed in preservative fluid with the idea of delaying their exhibition until the subject has been thoroughly worked up. Doubtless each of us has, with the best intentions in the world, set aside many of these specimens,

and has not been able, owing to the press of other work, to present them in a completely worked-up form. Even though the specimens are ultimately shown they cannot be exhibited to as great an advantage after the use of preservatives as shortly after their removal. It is a pity that some provision is not made by which an exhibition of such specimens preliminary to the final report might be made. Such an exhibition would not interfere with the ultimate more careful study of the case, and would certainly be to our advantage. Many specimens are removed which are too commonplace to make us think of writing out a detailed report of the case, or of announcing the exhibition of the specimen, yet we can never see too much of the ordinary lesions encountered in the routine making of autopsies. Some such plan as the Business Committee attempted to adopt two years ago, by which specimens could be arranged in a manner to permit of their ready inspection, with an accompanying card giving a brief description of the specimen, and possibly some points in the clinical history, would certainly be an advantage. If one of us has a well-marked instance of some such lesion as mitral stenosis or cirrhosis of the liver, he is apt to neglect showing it at the Society meetings because he feels that there is nothing particular to say about it that would warrant its announcement on the program. From the interest manifested by the members of the Society in coming forward to look at specimens of lesions which they have frequently seen before, I do not doubt that a table covered with card specimens would attract a considerable amount of attention and add to the interest of the meetings. These could be examined either before the meeting, after the meeting, or during the times when others are crowding around specimens illustrating a paper which has just been presented. I am sure that with the plan once carried out for a few meetings, not only would the number of card specimens steadily increase, but the members would feel a new interest in coming to the meetings.

While our life during the past year has been a successful one, it has in other ways been an unfortunate year for the Society. During the past twelve months we have lost by death four of our former Presidents, Alfred Stillé, J. M. Da Costa, John Ashhurst, Jr., and E. O. Shakespeare. Proper action upon their death will be taken by

committees appointed by direction of the Society, but I cannot refrain here from merely alluding to the loss of four men who, though for some time taking no active part in the Society's transactions, have in the past largely contributed to its success and been an honor to its membership-roll. Another member of the Society whose death has occurred within the last year is Thomas S. Kirkbride, Jr. With his intense enthusiasm, his thorough training, and the advantages which he had taken of his opportunities, we may feel sure that had he lived he would have taken a leading part in our proceedings. Even as it is, I cannot but feel that his interest in his profession has had an influence for good upon those of us who were thrown with him, and that the work which he started with so much zeal in the laboratory of which he was the head will be productive of good and lasting results.

In closing, I would merely express the pleasure that I have felt in presiding over the meetings of the Pathological Society and my appreciation of the honor that has been conferred upon me in allowing me the privilege of serving in the same position that has in the past been adorned by so many illustrious names of Philadelphia physicians.

October 11, 1900.

Nature and Distribution of the New Tissue in Cirrhosis of the Liver. (Preliminary Communication.)

SIMON FLEXNER, M.D

Much has been written upon the histologic changes of the liver in cirrhosis. The main attention, however, has been paid to the problem concerning whether the interstitial elements or the liver cells are primarily affected. Hitherto it has been deemed sufficient to speak of the increased interstitial tissue simply as connective tissue. The introduction of specific stains, especially in the last two years, for demonstrating elastic tissue has made it possible to determine what part of this so-called connective tissue is of the nature of the former tissue. The application, moreover, of certain dissociating technic methods previously employed in purely histologic studies to the elucidation of the same problem has also led

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to the further differentiation of the several tissues concerned in the production of the "fibrosis" of cirrhosis.

That white fibrous tissue is contained in the human liver, especially in the interlobular spaces, has, of course, been known for many years, but that reticulum is also a regular constituent of this organ and permeates the lobules we have come to know since the studies of digestion by Mall (*Johns Hopkins Hospital Reports*, vol. i. p. 171). We may, however, say that, so far as the technic methods are capable of indicating at this time, there is evidence of the occurrence of the three several kinds of connective tissue—white fibrous tissue, elastic tissue, and reticulum—within the liver, but that the distribution of the tissues varies. The ordinary white fibrous tissue is found with the bloodvessels, being therefore chiefly marked and in the largest quantity in the interlobular spaces. Reticulum, on the other hand, occurs especially within the lobule; the fibrils are fine, and not usually demonstrable in stained preparations. The elastica in the normal organ is present chiefly within and about the bloodvessels. It occurs also, as will be seen, in Glisson's and the surface capsules and in the bile-ducts.

The quantity of elastic tissue varies with the age of the individual. In children it is present in less amount than in middle age, and in the latter it is less abundant than in old age. The chief elastic tissue is contained in the bloodvessels and in Glisson's capsule, but it is found in the hepatic vessels and their branches, with the exception of the central veins, where it is usually absent, or, if present at all, it occurs in very small amount.

The hepatic arteries and portal veins contain a well-developed elastic membrane in the adventitial coats, the fibers composing the network being quite uniform in size. The muscular coats, especially of the arteries, are relatively free from fibers. The bile-ducts, on the other hand, are distinguished from the bloodvessels, inasmuch as the layer of elastic tissue in the wall next the epithelium consists of a very delicate fibrillar network, while in the external layer, which corresponds with the adventitia of the bloodvessels, a thicker network occurs. A cross section through the interlobular vessels shows that the elastica of the external layer of the portal vein, hepatic artery, and bile-ducts unite into a network which surrounds, as a general capsule, the interlobular

vascular system. Neither the surface nor the interlobular capsule sends elastic fibers into the interior of the lobules. The stroma of the lobules in normal organs consists solely of collagenous tissue.

Our knowledge of the distribution of the elastic tissue in the liver, both in health and in disease, we owe to the studies of Melnikow-Raswedenkow (*Ziegler's Beiträge*, 1899, xxvi. p. 526). The studies made by him upon such pathologic conditions as atrophy, chronic congestion, and cirrhosis have led him to conclude that in chronic morbid hepatic processes associated with an overgrowth of connective tissue, the overgrowth is chiefly composed of elastic tissue. In simple atrophy of the organ the elastic tissue develops in the periphery where the atrophy usually begins.

Cirrhosis—atrophic, mixed, and hypertrophic—gives rise to various grades of the new formation of elastic tissue, depending upon the degree of the atrophy, the duration of the process, and probably its nature. More elastic tissue is found in the atrophic cirrhosis than in the mixed, and more in this than in the hypertrophic. The elastica uses the interlobular vessels, especially arteries, portal veins, and bile-ducts for its origination, but sometimes the hepatic veins are employed. The elastic elements are found especially in Glisson's capsule, but sometimes they penetrate into the acini between the rows of liver cells.

The studies which shall be reported briefly in this paper were carried out in the Pathological Laboratory of the University of Pennsylvania by Drs. Hatfield and Goepp. They had for their thesis the determination of the nature and distribution of the newly-formed tissue in cirrhosis. Account was taken not only of the normal and pathologic distribution of the elastic tissue, but equally of the white fibrous tissue and reticulum. Commonly the three tissues were followed in the same organ, and a comparison of the results of the use of special technic methods as applied to them was made.

METHODS OF STUDY. *Elastica.* Two methods are now open to use for the demonstration of this tissue, both being in the nature of specific stains; the first is that of Unna, in which orcein is employed, and the other that of Weigert, which employs a resorcin and fuchsin combination. The early experiments with Unna's method were very unsatisfactory, because it was found that the

staining was irregular and inconstant. On the other hand, Weigert's method gave from the beginning a constant result; it was therefore employed to the exclusion of the former method.

In the study of the amount and distribution of the elastic tissue, recourse was had to the method of digestion, for the purpose of controlling the results obtained with Weigert's stain. Inasmuch as elastica quickly disappears under the influence of pancreatic digestion that element could easily be eliminated, while the remaining connective tissues were retained in the sections, thus affording a check upon the perfection of the selective stain.

Reticulum. For the purpose of demonstrating the tissue within the lobules of the liver, the digestive method, as first introduced by Mall, as well as the modification of Spalteholz were utilized. By these methods both fresh and preserved tissues in sections are digested in an alkaline solution, by means of pancreatin, when the parenchymatous cells and the elastic tissue are completely removed. There remains behind a framework consisting of white fibrous tissue and reticulum. Mall has shown us what the normal intralobular distribution of the reticular tissue is. Comparisons are easily made between the normal and the pathologic condition as found in cirrhosis.

White Fibrous Tissue. In the study of the white fibrous tissue of the liver, stained sections, both before and after digestion, were employed. Beside the ordinary stains for that tissue, and the reticulum stains which also color it, the recent specific stain of Mallory was employed. The last staining method was found especially useful in demonstrating the fine fibrils of white fibrous tissue contained within the liver lobules; but inasmuch as this stain also colors the reticulum, its use is somewhat more limited than could be wished; on the other hand, it apparently leaves the elastic fibers unaffected. Attempts were made to eliminate the white fibrous tissue by digestion in caustic alkaline solutions, but with very imperfect success.

Elastica. For the purpose of studying the pathologic distribution of this tissue well-marked examples of cirrhosis, both atrophic and hypertrophic, as well as specimens of the liver which macroscopically appeared normal, but in which a slight proliferation of cells in interlobular tissue had taken place, were employed.

ATROPHIC CIRRHOSIS. In a case of nodular cellular new growth small accumulations of lymphoid cells occur in the interlobular tissue. These foci of cells are usually quite small and do not penetrate into the lobules. There is a very slight, indeed, almost unappreciable, growth of ordinary fibrillated connective tissue within these nodules. On the other hand, finer and coarser fibrils of elastic tissue appear among the cells. The larger the periportal space the coarser the fibrils that occur in the cellular nodules. In another specimen of localized interlobular increase in the connective tissue, in which, however, the new tissue is very poor in cells, there is a very marked increase in elastic tissue. This tissue forms a quite uniformly meshed network, surrounding the vessels and extending throughout the connective-tissue growth. There is in this case almost no attempt to invade the intralobular tissue. In marked examples of perilobular cirrhosis specimens stained for elastic tissue, and observed by the naked eye, present an insular appearance. The islands are pale in appearance, vary in size from a fraction of a lobule to several lobules, and are separated by dark lines of elastic tissue. Microscopic examinations show that these dark bands correspond partially with the hypertrophied strands of Glisson's capsule, some, however, proceeding from the surface capsule and extending into the liver substance.

The indentations of the surface correspond with the depressed masses of fibers. There is a continuation of the elastic tissue in the capsule with the invading processes within the liver. The fibers in the capsule are arranged in the form of a crenated and closely woven network. A similar structure is apparent in the continuation within the liver. Newly-formed and dilated bloodvessels, the walls of which are composed of such fibrillated tissue, are associated with the new growth. In some places the new tissue within the liver substance consists of very closely anastomosing bands, in the midst of which are the remnants of liver lobules. Not all of the dense tissue stains sharply, but the sharply stained fibers have the same meshed and crenated appearance as is seen about the capsule, and they proceed from the walls of bloodvessels and bile-ducts. In the specimen being described there are a fair number of so-called newly-formed bile-ducts; these, it should be emphasized, differ from the normal bile-ducts

in that they present an imperfect development of elastic tissue about them, or they may be entirely deficient of such fibers. It is evident from the specimens that much of the new growth of interlobular tissue is not, properly speaking, elastic tissue. The new formation of elastic tissue in this form of cirrhosis does not remain limited to the periportal tissues. Just as in this condition the ordinary connective tissue invades the lobules, so may the elastic tissue appear in that situation. The degree of invasion is variable, but in such specimens as I have examined it is not common to find much new elastic tissue within the lobules unless these structures have been more or less completely destroyed by the new growth of tissue. The elastic tissue penetrates along the line of liver cells, usually in the form of fine bands or strands. In an instance of perilobular cirrhosis in which there was much cellular infiltration and penetration of the small cells, in the form of nodules into the lobules, fine, wavy, and anastomosing fibrils of the elastic tissue were present within the intralobular cellular accumulations.

HYPERTROPHIC CIRRHOSIS. The changes in this condition, which will be described, are based upon a small number of cases in which the livers were markedly enlarged and the surface smooth or very slightly indented. Weigert's stain indicates that much of this tissue is composed of elastica, which is present in the form of bands, composed of branching, anastomosing fibers, many of them either starting from or reaching the surface capsule. Where indentations of the surface are present they correspond with these bands. The sections are cut up into irregular islands of pale color by the bands of blue-stained fibrils which proceed from the interlobular tissue. In addition to these grosser bands, fine wavy lines extend into the lobules, subdividing these units into much smaller units, composed of a few liver cells or even single cells. The fibrils last described often suggest continuity with the reticulum and the capillary walls that exist between the rows of liver cells. This intralobular growth may be extremely fine and very diffuse, so that the impression is obtained that a large part of the increase in size of the liver is brought about by this intercalation. The very minute fibers come out with such distinctness as to suggest that they might have been drawn with a pen.

Reticulum. For the study of the changes in the reticulum, several different specimens of atrophic and two specimens of hypertrophic cirrhosis were employed. The fresh tissue was studied by Mall's method, and the hardened tissue by the method of Spalteholz.

ATROPHIC CIRRHOSIS. In an extreme grade of this form of cirrhosis digested specimens show a very large amount of new tissue in the periphery of the lobules and an intralobular invasion of coarse fibrils derived immediately from the extralobular growth. Wherever the lobules have been greatly encroached upon the reticulum is correspondingly reduced in volume; but what remains has not necessarily undergone any change in arrangement and in the size of the individual fibrils. On the other hand, the ingrowth of white fibrous tissue would appear to take place in such a way as to utilize the arrangement afforded by the reticular fibers. At first sight it might be supposed that the coarse fibers just mentioned are a modified reticulum, but serial sections show that they are connected with the peripheral new growth of tissue. The great difficulty of separating by chemical means reticulum and white fibrous tissue makes it impossible to say whether, after all, some of the coarser fibers within the lobules in this case may not be reticulum. What is, however, very important, and should be emphasized, is that after digestion and the elimination of all of the elastic fibers there still remains behind a large amount, indeed, apparently as large a volume as before, of collagenous fibrils.

In other specimens in which the perilobular growth is less marked than in the previous instance, interesting changes were made out in the reticulum. In these specimens there is little or no invasion from without. The architecture of the reticulum is preserved in its normal arrangement, but the individual reticular fibers are hypertrophied, the greatest degree of thickening occurring in the periphery near the thickened interlobular tissue. While equally hypertrophied fibers are also found well removed from the peripheries in the centers of the lobules, yet at the same time I prefer to speak guardedly with reference to their ultimate nature. I think it possible that the fibers have proceeded from the interlobular tissue, in which case they are not, *a priori*, to be regarded

as reticulum. On the other hand, if these fibers are of the nature of white fibrous tissue, they represent an intralobular invasion from the periphery, which ordinary methods would not expose. It should be mentioned here that the study of the finer intralobular growth of the connective tissue is likely to be much facilitated by the new staining method for fibrous tissue recently introduced by Mallory (*Journal of Experimental Medicine*, 1900, vol. v., No. 1).

HYPERTROPHIC CIRRHOSIS. The limited number of specimens (2) which have been open to study will not permit of any far-reaching conclusions being drawn. The main alterations, as shown by these cases, consist of a much more moderate new growth of tissue in the periphery of the lobules and a finer invasion of the lobules than in the previous class of cases. The difference between the original reticular fibers and the newer fibers is easily made out by the relative coarseness of the fibers and by their arrangement. While in a general way they follow the arrangement of the reticulum, they are in places so increased as to obliterate the original architecture, and, in addition, they come together in what might be termed centers, from which the fibers radiate in all directions. These stellate centers form a good index of the degree of lobular invasion.

White Fibrous Tissue. This tissue has been considered in two previous sections. All attempts to eliminate it from the preparations by means of caustic alkalies were more or less unsuccessful. By exclusion of the elastic element, on the one hand, and the consideration of the reticulum on the other, the conclusion was reached that white fibrous tissue is a constant and abundant constituent of all forms of marked cirrhosis, that in certain very cellular examples it is present in small amount, and perhaps is exceeded by the elastic element; but, on the other hand, wherever fibrillated tissue is present to any extent, notwithstanding the presence of elastica in large amount, there is also present equally large or larger amounts of white fibrous tissue.

CONCLUSIONS. 1. In all forms of cirrhosis the white fibrous tissue is increased.

2. Along with the increase of white fibrous tissue there is a new formation of elastic tissue. This new elastic tissue is derived

from pre-existing tissue in the adventitia of bloodvessels and the hepatic capsule.

3. Both white fibrous tissue and elastic tissue, in all forms of cirrhosis, may penetrate into the lobules. This penetration takes place along the line of capillary walls or follows the architecture of the reticulum. The chief distinctions between the histology of atrophic and hypertrophic cirrhosis depends upon the degree of extralobular growth and the freedom with which the lobules are invaded. In hypertrophic cirrhosis there would appear to be less interlobular growth and an earlier and finer intralobular growth.

4. The alterations in the reticulum, *per se*, consist, as far as can be made out at present, of hypertrophy rather than hyperplasia of the fibers. It is still uncertain whether any of the differential methods now in use suffice to distinguish between the reticulum and certain fibers derived from the white fibrous tissue of the periphery of the lobules.

May 24, 1900.

The Effect of Cold Upon the Vitality of the Bacilli of Bubonic Plague.

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(Communicated through SIMON FLEXNER, M.D.)

In the autumn of 1899 a Japanese Medical Commission was dispatched, at the request of the International Sanitary Board, to New Chwang, a port in the northern portion of China, for the purpose of combating the plague which had prevailed there since the end of the summer.

At the time of our arrival the winter season was approaching and the epidemic diminishing in severity, so that I was able to see only 11 cases, 7 of which were of the pneumonic and 4 of the bubonic form.

The winter of our stay was of the severe Manchurian type, and the river Laio was sealed with ice. The conditions seemed favor-

able for testing the resisting power of the plague bacilli against cold. Hitherto the experiments respecting the resistance of these organisms had been made for the greater part with heat, though a few of these, of an unsatisfactory character, had been made with extremes of cold. Inasmuch as I utilized the natural cold, it was manifestly impossible to obtain a constancy of temperature, so that I noted the extremes, viz.: the maximum and the minimum of the days on which the experiments were performed. The thermometers employed were obtained from the Custom House, consisting of two sets; these were observed at intervals of three hours.

The material used for the experiments was obtained from two cases, one of which was of the pure pneumonic type, and the other also pneumonic but associated with buboes.

Pure culture upon agar-agar and bouillon which had been incubated for forty-eight hours at 35° C. were exposed to cold. In addition to these experiments, a third series in which the semi-dry material was smeared upon cover-glasses was employed. The several kinds of material were exposed in a place free from the sun. A determination of the viability was made by transplanting, out of each culture, large blocks of colonies upon culture media, which were placed in the incubator.

The experiments covered a period of three weeks, from January 9th to 29th, 1900. One of the necessary conditions of the experiments is the demonstration of the agar as suitable to the growth of the bacilli. This precaution was not omitted. In the case of the smear preparations, the cover-glasses were placed in nutrient media immediately after the exposure. The following table gives the results of the experiments:

| Date. | Temperature. | | Exposure time. | Results. | | |
|-----------------|--------------|-----------|----------------|----------|----|----|
| | | | Days. | A. | B. | C. |
| January 9 . . . | -4° F. | -15.5° C. | 1 | + | + | + |
| 10 . . . | -1 | -18.5 | 2 | + | + | + |
| 11 . . . | -7 | -21.5 | 3 | + | + | + |
| 12 . . . | -4 | -20 | 4 | + | + | + |
| 13 . . . | -9 | -23 | 5 | + | + | + |
| 14 . . . | -10 | -23.5 | 6 | + | + | + |
| 15 . . . | -7 | -21.5 | 7 | + | + | + |
| 16 . . . | -9 | -23 | 8 | + | + | + |
| 17 . . . | -10 | -23.5 | 9 | + | + | + |
| 18 . . . | -0 | -18 | 10 | + | + | + |
| 19 . . . | 10 | -12 | | | | |
| 20 . . . | -2 | -19 | | | | |
| 21 . . . | -2 | -19 | | | | |
| 22 . . . | -6 | -21 | 2 weeks | + | + | + |
| 23 . . . | -5 | -20.5 | | | | |
| 24 . . . | -10 | -23.5 | | | | |
| 25 . . . | -8 | -22 | | | | |
| 26 . . . | -11 | -24 | | | | |
| 27 . . . | -8 | -22 | | | | |
| 28 . . . | -8 | -22 | | | | |
| 29 . . . | 7 | -14 | 3 weeks | + | + | + |

From these experiments it can be concluded that whereas the plague bacilli are devitalized at 60° C., that is 20° above the maximum temperature of development, a corresponding extreme below the minimum limit of multiplication, viz. : -20° C., does not cause a similar destruction.

Incidentally I have experimented to determine the effect of drying upon the vitality, and have found that a temperature of 35° C. continued for twenty-four hours suffices to kill the bacilli when suspended within a thin stratum upon cover-glasses.

The conclusion to be drawn is that plague bacilli contained within fluid or solid media, or in the semi-dried state, survive temperatures ranging from -5° C. to -24° C. after an exposure of at least three weeks.

October 25, 1900.

Cerebral Hemorrhage.

AUGUSTUS A. ESHNER, M.D.

J. C., a white woman, forty years old, was admitted to the Philadelphia Hospital on August 8, 1900, presenting left hemiplegia of 'three days' standing, which had developed after what was described

as a "fainting spell," unattended with loss of consciousness or fall. The face was not involved, nor was the tongue. Urine and feces were voided involuntarily. The patient exhibited also delusions and hallucinations, and she talked a good deal and incoherently. The pupils were equal and reacted to light. The reflexes could not be elicited on the left side, and sensibility appeared at first to be abolished, and subsequently delayed. Examination of the urine disclosed on one occasion the presence of albumin and granular casts, and on another occasion no abnormal condition.

The temperature fluctuated for a few days between 100° and 102.5° , then for a few days more between 99° and 101° , becoming normal on the ninth day and subnormal on the thirteenth day, at which level it continued, with exacerbations to the normal on the day of death. Toward the termination of the case the pulse and respiration became accelerated.

Death resulted fifteen days after admission. On postmortem examination the body was found to be that of an obese, muscular woman. The left ventricle was hypertrophied, but otherwise the heart was normal. The kidneys were fatty and the seat of cysts, and the cortex was thickened. The calvarium, the dura, and the pia presented nothing noteworthy. Pressure on the brain developed slight, deep-seated fluctuation, while pressure on the corpus callosum developed marked fluctuation. Both ventricles, when opened, were found enormously dilated. No gross lesion was found in the left hemisphere, but in the right was a large hemorrhage the size of an egg, destroying the basal ganglia, and showing in part distinctly through the ependyma.

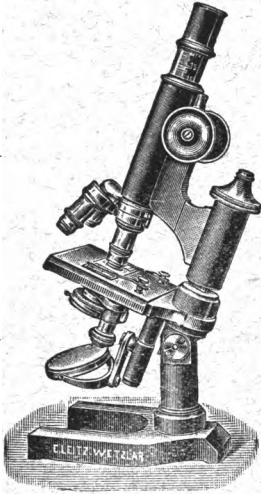
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